Sisson, Bradley

From:	Todd Armstrong [tarmstrong@clarkelbing.com]
Sent:	Wednesday, March 12, 2008 10:11 AM
To:	Sisson, Bradley
Cc:	Kristina Bieker-Brady; Sarah Wilcox; KBBAssistants
Subject:	RE: U.S. Serial No. 10/070,297; METHODS UTILIZING DIFFERENTIAL SPLICING EVENTS IN BLOOD CELLS FOR THE DETECTION OF PATHOLOGICAL EVENTS; Our Ref. No.: 50146/002002
Importance:	High
Attachments:	50146.002002 Proposed Supplemental Amendment 03.12.08.doc

Dear Examiner Sisson:

Further to our telephonic communication of February 8, 2008, we attach for your review a draft supplemental amendment in connection with the above-referenced application. In addition to the claim amendments, we provide remarks distinguishing the method of present claims 27, 30-33, 44, and 47-53 over Brennan et al. (U.S. Patent No. 5,474,796), which was raised during our discussion.

Kindly review the proposed amendments and let us know if you agree that the claims are in condition for allowance. As you know, the final deadline for responding to the outstanding Office Action is March 20, 2008. Therefore, we kindly request your comments in advance of that deadline.

Very truly yours,

Todd

Todd Armstrong, Ph.D.
Patent Agent

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110

Telephone: 617-428-7036
Facsimile: 617-428-7045

DRAFT

PATENT
ATTORNEY DOCKET NO. 50146/002002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Tocque et al.	Confirmation No.:	2833
Serial No.:	10/070,297	Art Unit:	1634
Filed:	March 5, 2002	Examiner:	Bradley L. Sisson
Customer No.:	21559		
Title:	METHODS UTILIZING DIFFERENTIAL SPLICING EVENTS IN BLOOD CELLS FOR THE DETECTION OF PATHOLOGICAL EVENTS (As Amended)		

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL AMENDMENT

Applicants submit the following supplemental amendment in response to the telephonic interview of February 8, 2008. Applicants kindly request the Examiner's consideration of the supplemental amendment.

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AMENDMENT TO THE CLAIMS

This listing of claims will replace all prior versions of claims in the application:

Listing of Claims:

1-26 (Cancelled)

27. (Currently Amended) A method for the detection *in vitro* of a given, predefined pathological condition associated with a deregulation in a cell signaling pathway in a human subject, wherein said given, predefined pathological condition ~~is a pathological condition that~~ causes disease in a tissue distinct from nucleated blood cells of said human subject, said method comprising:

(i) providing a sample ~~of~~ comprising nucleated blood cells from the subject being tested for the presence of said pathological condition, ~~wherein said blood cells comprise lymphocytes, macrophages, monocytes or dendritic cells,~~

(ii) preparing nucleic acid molecules from the sample of step (i),

(iii) hybridizing all or part of the nucleic acid molecules from step (ii) to at least one nucleic acid library capable of detecting the presence of said given, predefined pathological condition when contacted with a diverse population of nucleic acid molecules prepared from nucleated blood cells from a human subject having said given, predefined pathological condition under conditions allowing hybridization to occur, said library having an ordered arrangement on a support and comprising a plurality of nucleic acid molecules that specifically hybridize to differentially spliced ribonucleic acid molecules (RNAs) expressed in nucleated blood cells from human subjects known to have said given, predefined pathological condition, wherein said ~~blood cells comprise lymphocytes, macrophages, monocytes, or dendritic cells and said~~ differentially spliced RNAs are ~~having an ordered arrangement on a support to obtain a first hybridization profile, wherein~~

~~(a) said plurality of nucleic acid molecules are specific for differentially spliced ribonucleic acid molecules (RNAs) expressed in blood cells from human subjects known to have the given, predefined pathological condition,~~

~~(b) the presence of said differentially spliced RNAs being~~ characteristic of said

given, predefined pathological condition that causes disease in a tissue distinct from nucleated blood cells, and

~~(c) said blood cells from human subjects known to have said given, predefined pathological condition comprising lymphocytes, macrophages, monocytes, or dendritic cells, and~~

(iv) detecting hybridization between a plurality of said nucleic acid molecules of said subject being tested and said nucleic acid molecules of said library, wherein said hybridization indicates ~~correlating the first hybridization profile with a second hybridization profile obtained by hybridizing nucleic acid molecules from blood cells of a subject known to have said given, predefined pathological condition to said nucleic acid library, thereby indicating~~ the presence of said given, predefined pathological condition in said subject being tested.

28-29 (Cancelled)

30. (Previously Presented) The method of claim 27, wherein the nucleic acid molecules prepared from the sample are total or messenger RNA or complementary deoxyribonucleic acid (cDNA) derived therefrom.

31. (Previously Presented) The method of claim 30, wherein the nucleic acid molecules prepared from the sample are amplified.

32. (Currently Amended) The method of claim 27, wherein the nucleic acid molecules prepared from the sample are labeled.

33. (Previously Presented) The method of claim 27, for the detection *in vitro* of the stage of progression of said given, predefined pathological condition in said subject.

34-43 (Cancelled)

44. (Previously Presented) The method of claim 27, wherein said support is a

membrane, a glass plate, or a biochip.

45-46 (Cancelled)

47. (Previously Presented) The method of claim 27, wherein said pathological condition is characterized by an excessive cell proliferation.

48. (Currently Amended) A method for the detection *in vitro* of a given, predefined pathological condition characterized by an excessive cell proliferation in a human subject, wherein said given, predefined pathological condition ~~is a pathological condition that~~ causes disease in a tissue distinct from nucleated blood cells of said human subject, said method comprising:

(i) providing a sample ~~of~~ comprising nucleated blood cells from the subject being tested for the presence of said pathological condition~~, wherein said blood cells comprise lymphocytes, macrophages, monocytes or dendritic cells~~,

(ii) preparing nucleic acid molecules from the sample of step (i),

(iii) hybridizing all or part of the nucleic acid molecules from step (ii) to at least one nucleic acid library capable of detecting the presence of said given, predefined pathological condition when contacted with a diverse population of nucleic acid molecules prepared from nucleated blood cells from a human subject having said given, predefined pathological condition under conditions allowing hybridization to occur, said library having an ordered arrangement on a support and comprising a plurality of nucleic acid molecules that specifically hybridize to differentially spliced ribonucleic acid molecules (RNAs) expressed in nucleated blood cells from human subjects known to have said given, predefined pathological condition, wherein said ~~blood cells comprise lymphocytes, macrophages, monocytes, or dendritic cells and said~~ differentially spliced RNAs are ~~having an ordered arrangement on a support to obtain a first hybridization profile, wherein~~

~~(a) said plurality of nucleic acid molecules are specific for differentially spliced ribonucleic acid molecules (RNAs) expressed in blood cells from human subjects known to have said given, predefined pathological condition,~~

~~(b) the presence of said differentially spliced RNAs being~~ characteristic of said given, predefined pathological condition that causes disease in a tissue distinct from nucleated blood cells, and

~~(c) said blood cells from human subjects known to have said given, predefined pathological condition comprising lymphocytes, macrophages, monocytes or dendritic cells, and~~

(iv) detecting hybridization between a plurality of said nucleic acid molecules of said subject being tested and said nucleic acid molecules of said nucleic acid library, wherein said hybridization indicates ~~correlating the first hybridization profile with a second hybridization profile obtained by hybridizing nucleic acid molecules from blood cells of a subject known to have said given, predefined pathological condition to said nucleic acid library, thereby indicating~~ the presence of said given, predefined pathological condition in said subject being tested.

49. (Previously Presented) The method of claim 48, wherein said given, predefined pathological condition characterized by an excessive cell proliferation is stenosis.

50. (New) The method of claim 48, wherein said nucleated blood cells comprise lymphocytes, macrophages, monocytes or dendritic cells.

51. (New) The method of claim 48, wherein said nucleic acid library further comprises a control nucleic acid molecule.

52. (New) The method of claim 27, wherein said nucleated blood cells comprise lymphocytes, macrophages, monocytes or dendritic cells.

53. (New) The method of claim 27, wherein said nucleic acid library further comprises a control nucleic acid molecule.

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REMARKS

Applicants wish to thank Examiner Sisson for the telephonic interviews of December 4, 2007, and February 8, 2008. Applicants have further amended independent claims 27 and 48 and added new claims 50-53 and believe that present claims 27, 30-33, 44, and 47-53 are now in condition for allowance. [1]

For the reasons previously given, Varesco et al. (Hum. Genet. 93:281-286, 1994) and Morris et al. (U.S. Patent No. 5,770,421) fail to teach or suggest a method for detecting a pathological condition of a tissue distinct from blood cells by using nucleic acid molecules obtained from blood cells. For the reasons given below, Brennan et al. (U.S. Patent No. 5,474,796), which was cited by the Examiner during the telephonic interview of February 8, 2008, fails to remedy the deficiencies of Varesco et al. and Morris et al.

Brennan discloses an "apparatus and methods for making arrays of functionalized binding sites on a support surface…for sequencing oligonucleotides" (Abstract). The apparatus prepared by the Brennan method "contains oligonucleotides having 10 nucleotides each (10-mers)…In this way the total array represents every possible permutation of the 10-mer oligonucleotide" (see col. 9, line 48, through col. 20, line 5). Brennan fails to teach or suggest an apparatus having a nucleic acid library that is capable of detecting the presence of a given, predefined pathological condition when contacted with a diverse population of nucleic acid molecules prepared from nucleated blood cells from a human subject having the given, predefined pathological condition under conditions allowing hybridization to occur, as is required by the method of present independent claims 27 and 48. Instead, the Brennan apparatus, because it includes every permutation of 10-mer nucleic acid sequences, would bind *every species* of nucleic acid molecule present in a sample when it contains a diverse population of nucleic acid molecules, e.g., cDNA molecules prepared from nucleic acid molecules from nucleated blood cells of a subject, even those nucleic acid molecules not indicative of a given, predefined pathological condition.[2] Thus, the Brennan apparatus would be incapable of

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[1] Support for new claims 50 and 52 is found in the specification at, e.g., page 6, line 26, through page 7, line 14. Support for new claims 51 and 53 is found in the specification at, e.g., page 20, lines 1-4. No new matter is added by the amendment.

[2] In fact, Brennan et al. clearly discloses that only a single species of "target nucleic acid" is to be applied

detecting whether a sample containing a diverse population of nucleic acid molecules contains differentially spliced ribonucleic acid molecules (RNAs) indicative of a given, predefined pathological condition, as is required by the method of present independent claims 27 and 48, and claims dependent therefrom. Accordingly, Brennan et al. does not remedy the deficiencies of Varesco et al. and Morris et al.

CONCLUSION

Applicants submit that present claims 27, 30-33, 44, and 47-53 are now in condition for allowance. Applicants respectfully request that the Examiner contact the undersigned should there be any remaining issues that require resolution.

Respectfully submitted,

Date:_____

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Kristina Bieker-Brady, Ph.D.
Reg. No. 39,109

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

to the Brennan apparatus and not a diverse population of nucleic acid molecules because the purpose is to sequence the target nucleic acid molecule (see Example 4 of Brennan et al.).